1.0 SCIENTIFIC ABSTRACT OF THE PROTOCOL

Cystic fibrosis (CF), the most common lethal genetic disease in North America, is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene product is required for regulation of epithelial chloride transport in multiple organs, including the airways. CF lung disease develops gradually over many years as abnormally viscous secretions lead to airway obstruction, infection, inflammation, and fibrosis. It ultimately may lead to respiratory failure, which is the cause of death in more than 90% of CF patients. It is thought that correction of the underlying CFTR gene defect may result in therapeutic effect on the progressive lung disease.

Targeted Genetics Corporation has developed a vector system for CFTR gene transfer, tgAAVCF, which is based on the non-pathogenic adeno-associated virus (AAV). AAV vectors can stably persist in the host cell, and AAV-CFTR vectors have been shown to confer long-term correction of the physiologic defect in cAMP-mediated chloride secretion when administered to cultured CF bronchial epithelial cells. Furthermore, AAV-CFTR vectors transduce and express recombinant CFTR *in vivo* after delivery to the airway surface of animals. Long-term vector expression, up to 6 months after a single-dose administration, has been observed in the New Zealand white rabbit and rhesus monkey models. Studies of tgAAVCF administered to the sinuses of patients with cystic fibrosis have shown lack of toxicity, persistent gene transfer, and statistically significant changes in the transepithelial potential difference of the epithelial monolayer lining the sinus. Studies of tgAAVCF in the nose and the right lower lung lobe (delivered by bronchoscope) have demonstrated lack of toxicity, but have been at suboptimal doses for the evaluation of gene transfer and expression. Administration of higher doses of tgAAVCF by aerosol inhalation to rhesus macaques has demonstrated dose-dependent gene transfer and gene expression. Furthermore, the aerosol inhalation procedure was well-tolerated and administration of tgAAVCF was not associated with airway inflammation or any clinical toxicities or histopathology findings.

An additional advantage of AAV vectors is the absence of any wild-type AAV viral coding sequence in the vector construct. Inflammatory reaction as a result of viral gene expression is not a possibility with AAV-CFTR vectors because of their lack of viral genes. Studies in rabbits, mice, rats, rhesus macaques and humans have all demonstrated that single-dose AAV vector administration does not result in lung inflammation or any other adverse effects.

In this study, tgAAVCF is administered to CF patients with mild lung disease. This is a dose-escalation safety study of tgAAVCF vector administered by aerosol to the entire lung. Doses will range from 10^{10} to 10^{12} DNase resistant particles (DRPs). The primary objective of the study is to evaluate the safety of aerosolized tgAAVCF delivered to cystic fibrosis patients. Additional objectives of the study include evaluation of gene transfer and gene expression. The results of this study will serve to guide dosing and endpoints to be used in future clinical trials.